REMARKS

1. Preliminary Matters

a. Status of the Claims

Claims 25-27, 29-31, and 33 are pending this application. Claims 26, 29, and 33 were previously withdrawn from consideration, and the Examiner has now further withdrawn claim 30 from consideration. Claim 31 is amended to no longer depend from claim 30. Applicant respectfully requests entry of the amendments and remarks made herein into the file history of the application. Upon entry of the amendments, claims 25-27, 29-31, and 33 will be pending, and claims 25, 27, and 31 will be under active consideration.

b. Amendments to the Specification

Paragraph 0022 of the specification has been amended to incorporate by reference the substitute sequence listing submitted herewith.

c. Sequence Listing

On pages 5 and 6 of the Office Action, the Examiner alleges that the computer readable form (CRF) submitted on March 21, 2007 does not comply with 37 C.F.R. § 1.824(a)(1) because the CRF does not contain a single sequence listing. Applicant submits herewith in compliance with 37 C.F.R. §§ 1.821-1.825 a substitute sequence listing that spans three compact discs. In compliance with 37 C.F.R. § 1.824, Applicant also submits herewith a computer readable form that consists of a single compressed file contained on a single compact disc. In view of the substitute sequence listing and computer readable form, Applicant respectfully requests that the Examiner reconsider and withdraw the objection to the sequence listing and computer readable form.

d. Specification

On pages 6 and 7 of the Office Action, the Examiner objects to the specification because SEQ ID NO: 10068310 of the previously-filed sequence listing allegedly constitutes new matter. The substitute sequence listing submitted herewith does not contain this sequence, thereby rendering the Examiner's objection moot.

e. Information Disclosure Statement

On page 8 of the Office Action, the Examiner asserts that the information disclosure statement submitted on March 20, 2008 fails to comply with 37 C.F.R. §§ 1.97 and 1.98, and MPEP § 609 because the title of each publication listed in the information disclosure has not bee provided. Applicant submits herewith an information disclosure statement that lists the title of each reference, in compliance with 37 C.F.R. §§ 1.97 and 1.98, and MPEP § 609.

2. Patentability Remarks: 35 U.S.C. §§ 101 and 112, first paragraph

On pages 8-15, the Examiner rejects claims 25, 27, and 31 under 35 U.S.C. § 101 because the claimed invention allegedly is not supported by a credible asserted utility. Applicant respectfully disagrees. As acknowledged by the Examiner on page 8 of the Office Action, the asserted utility for the claimed nucleic acids is specific and substantial, and the utility rejection going forward is based on the alleged lack of credible utility.

On pages 14 and 15, the Examiner asserts that one of skill would have reason to doubt the objective truth of Applicant's asserted utility for the claimed subject matter without experimental validation. Applicant submits herewith experimental validation that the miRNA with the nucleotide sequence as set forth in SEQ ID NO: 7002375 (hsa-miR-494) is capable of regulating MAPKAPK2.

Specifically, Hep3B cells were transfected with an anti-sense oligonucleotide (ASO) that specifically binds to hsa-miR-494, and the amount of the miRNA target MAPKAPK2 was quantified using quantitative PCR (further details are shown in Appendix A). The amounts of mRNA for the ASO and no-ASO were each normalized according to the mRNA level of a housekeeping gene. The ASO to hsa-miR-494 led to an increase in the level of the mRNA of its target, as measured by cycle threshold.

Specifically, cells transfected with an ASO that targets hsa-miR-494 showed approximately a 3-fold increase in the level of MAPKAPK2 mRNA as compared to no-ASO control cells (Figure 1A; "ASO 494 24h" compared to "no treatment"). Accordingly, specifically inhibiting the activity of hsa-miR-494 (SEQ ID NO: 7002375) results in increased levels of its target mRNA. Therefore, one of skill would not doubt the objective truth of Applicant's asserted utility for the claimed subject matter because the utility of the claimed nucleic acids is firmly established by experimental evidence. In view of the foregoing, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 101. Additionally, because the claimed nucleic acids are supported by a specific, substantial, and credible utility, Applicant requests that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 112, first paragraph.

3. Conclusion

Applicant respectfully submits that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

POLSINELLI SHALTON FLANIGAN SUELTHAUS PC

Dated: August 1, 2008

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APPENDIX A

Target validation for miR-494

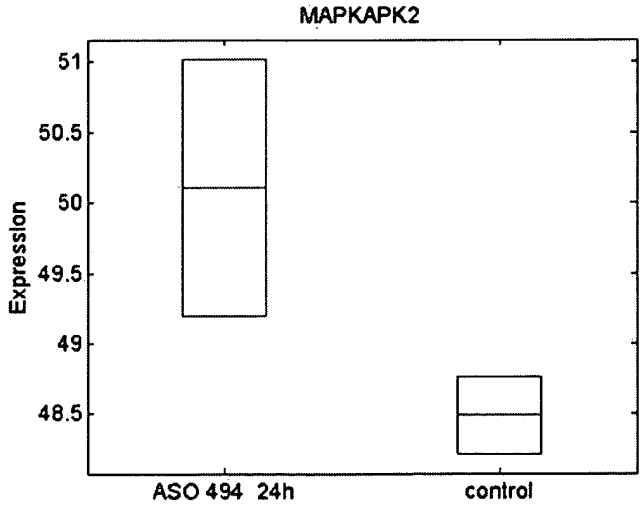
Brief description of the results:

Applicant has done RT-qPCR analysis for **hsa-miR-494** (SEQ ID NO.7002375), and its corresponding target **MAPKAPK2** (SEQ ID NO: 5210247, RefSeq NM_004759_) .

Cells were transfected with ASO to miR-494, for 24 and 48 hours. After transfection RNA was isolated and mRNA of MAPKAPK2 was quantified using specific primers by SYBR RT-qPCR method. Specifically RNA was reverse transcribed and 10ng of cDNA was used for qPCR reaction.

Measuring the amount of initial mRNA was based on the observation that the amount of cDNA generated from the mRNA doubles with every cycle of PCR. Therefore, after N cycles, there is 2^N times as much. In order to quantify the initial amount of mRNA, the cycle number at which the increase in fluorescence (and thus the amount of cDNA) was exponential, was measured. A threshold at this level of fluorescence was set. This threshold is indicated as the cycle threshold, or Ct. To compare the differences in quantity between a specific mRNA in two different samples, the Ct was calculated in each of the samples, and the delta Ct (dCT) was calculated. The fold-change between the amount of mRNA in the two samples was represented by 2^{dCt}.

Results of MAPKAPK2 expression with and without ASO to miR-494 are shown below:



- fold change for miR-494 is: 3 (*i.e.*, $2^{dCt} = 2^{(50.10-48.49)}$)
- the term "control" refers to untransfected cells.

The figure clearly shows that knocking down hsa-miR-494 by an ASO causes significant increase in the level of MAPKAPK2 mRNA, indicating that this miRNA regulates this gene's expression.

MATERIALS AND METHODS

Transfection and treatment of cells

Hep3B cells from the American Type Culture Collection (ATCC, Rockville, MD) were plated in 6-well plates 24 hrs prior to transfection or treatment. Cells were transfected with specific anti sense oligonucleotids (ASOs) to microRNA, from IDT, using Oligofectamine Invitrogen, Carlsbad, CA)). The reagents used for treatments were Interleukin - 6 (IL-6), Retinoic acid and Dexametazone. All treatments were done in duplicate. Previously those treatment were found to alter miRNA expression.

RNA Isolation and Reverse Transcription

Total RNA was isolated by EZ-RNA II kit (Biological Industries) 24 and 48 hrs after transfection. 1μg of total RNA was reverse transcribed using Superscript II.

Quantification by RT-qPCR

mRNA was quantified by real-time-qPCR SYBR Green method, using 7500 Fast Real time PCR system, AB applied Biosystems. Each test was done in triplicate. Ct values were normalized to TBP as a house keeping gene.

			Primers for Target	
miRNA	Target	ASO for miRNA	Fwd	Rev
hsa-miR-494	MAPKAPK2	GAGGTTTCCCGTGTATGTTTCA	ATCACCCCAAACAACTCAGC	TTCCCCCATACACAAAGACG
house keeping	TBP		TATAATCCCAAGCGGTTTGC	CACAGCTCCCCACCATATTC

STATISTICAL ANALYSIS

The statistical method used was a t-test (two-sided unpaired t-test) between the negative control and treated samples.

Normalization was done by subtracting the ct value of a house keeping gene-TBP. Ct value were determined using a default threshold of 0.2 in the 7500 Fast Real time PCR system, by ABI, and values were normalized to TBP as a house keeping gene.